2018 IEEE 15th International Symposium on Biomedical Imaging (ISBI 2018)
April 4-7, 2018, Washington, D.C., USA

DIFFERENTIATING TUMOR RECURRENCE FROM RADIATION-INDUCED NECROSIS: AN IMAGE-BASED MATHEMATICAL MODELING FRAMEWORK

Saramati Narasimhan[1], Michael I. Miga[1,2], Nitesh Rana[3], Haley B. Johnson[4], Albert Attia[3], Jared A. Weis[4,5]

[1]Biomedical Engineering, Vanderbilt University; [2]Vanderbilt Institute for Surgery and Engineering, Vanderbilt University; [3]Radiation Oncology, Vanderbilt University Medical Center; [4]Biomedical Engineering, Wake Forest School of Medicine, [5]Comprehensive Cancer Center, Wake Forest Baptist Medical Center

ABSTRACT

Patients with intracranial metastases often undergo stereotactic radiosurgery (SRS) for local control. Following SRS, some patients develop radiation-induced necrosis, which appears radiographically similar to tumor recurrence on follow-up imaging. Both may appear as an enhancing lesion in MR T_1-weighted contrast enhanced imaging with surrounding FLAIR abnormality, complicating diagnostic and therapeutic efforts. We develop a spatiotemporal model of tumor growth in this work to parameterize tumor growth kinetics, based on contrast enhanced T_1-weighted serial MR imaging. In a proof-of-concept study to demonstrate feasibility of the framework, we evaluated two patients, one with recurrence and one with radiation-induced necrosis. Model-data fits were used to parameterize tumor cell diffusion coefficient and tumor cell proliferation rate. Differences between the pathologies were found when comparing the tumor cell proliferation rate, suggesting the potential of this model to distinguish between diagnoses in a biophysical model-based image analysis framework.

***Index Terms*—** tumor, recurrence, radiation-induced necrosis, computational model, mathematical model

1. INTRODUCTION

Patients with metastatic cancer, resulting in intracranial metastases, are often treated with stereotactic radiosurgery (SRS). An adverse effect of SRS is radiation-induced necrosis, which occurs in up to 20% of patients [1]. This poses a significant clinical challenge as radiation-induced necrosis appears radiographically similar to tumor recurrence [1], resulting in complications for developing the patient treatment approach. The current gold standard for determining lesion etiology is biopsy [1], however in lieu of this invasive procedure, often, repeat serial follow-up imaging examinations are performed for clinical surveillance and observation of lesions with unknown etiology. Determining the nature of the lesion noninvasively would be a significant improvement in patient care in this challenging clinical setting.

There is a significant body of literature on the development and use of patient-specific tumor growth modeling, both in breast and brain tumors [2,3]. Some of these studies have also utilized imaging data to develop predictive models of tumor growth in order to assess therapy response and disease burden [2,3]. However, often the nature of computational oncological models relies on many assumptions of various biological parameters that are difficult, if not impossible to initialize and constrain [4]. In work reported herein, our focus was to develop a clinically-relevant framework, based solely on standard clinical imaging data, to generate a simple, translatable, and clinical workflow-friendly solution.

There have been several studies investigating mechanical stress as an inhibitor of tumor growth, indicating the significance of including mechanical stress in tumor growth models [5]. Our group has previously modeled tumor growth with a mechanically-coupled reaction-diffusion model, and performed investigations into the development of a predictive modeling framework to determine the response of breast cancer to neoadjuvant chemotherapy [6-8]. In that work, early cycle treatment changes were able to predict patients responsive to neoadjuvant chemotherapy [8]. In this work, we introduce the use of a similar mechanically-coupled reaction-diffusion modeling framework for patients with intracranial metastases to noninvasively distinguish between tumor recurrence and radiation-induced necrosis based on contrast enhanced T_1-weighted MR imaging.

2. MATERIALS AND METHODS

De-identified clinical data was obtained under a Vanderbilt University Institutional Review Board (IRB) approved exemption to analyze retrospective MR imaging data. For the purposes of this preliminary two-dimensional (2D)

investigation, serial MR imaging was obtained between the time of SRS and pathological confirmation of either tumor recurrence (1 patient) or radiation-induced necrosis (1 patient). In this work, the two contrast enhanced T_1-weighted MR scans acquired prior to pathological confirmation were used for both patients. The time between scans for the patient with confirmed tumor progression was 17.29 weeks, and the time between scans for the patient with confirmed radiation-induced necrosis was 1.43 weeks. The axial slice with the most radiographic volumetric change in the enhancing lesion was selected from registered images for 2D analysis.

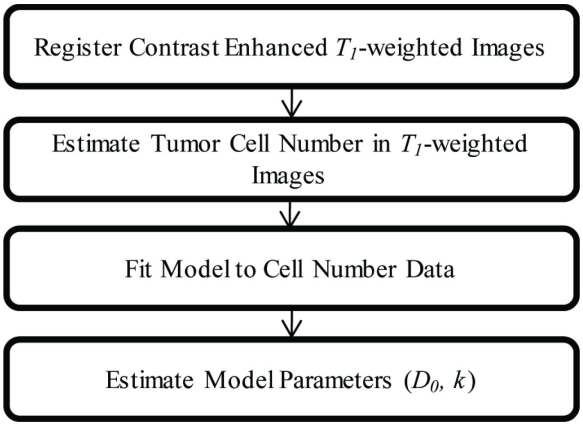

Figure 1. Schematic of parameter estimation framework.

A previously published mechanically-coupled reaction-diffusion model was used to model tumor growth [6-8]. While previous work utilized diffusion weighted MRI (DW-MRI) to estimate tumor cell density, due to the lack of available DW-MRI data in our clinical imaging database, we used an assumption of tumor cell distribution. We assumed that the enhancing lesion had a Gaussian distribution of tumor cell density, with a dense cellular core at the center at maximal cellular carrying capacity, θ, and density that decreased outwardly with a minimum tumor cell density of 25% of θ at the maximal long axis dimension of the lesion. The equations governing this model (Equations 1,2 and 3) are fully described in previous work [6-8]:

$$\frac{dN(\bar{x},t)}{dt} = \nabla \cdot \left(D\nabla N(\bar{x},t)\right) + kN(\bar{x},t)\left(1 - \frac{N(\bar{x},t)}{\theta}\right), \quad (1)$$

$$D = D_0 e^{-\gamma\sigma_{VM}(\bar{x},t)}, \quad (2)$$

$$\nabla \cdot G\nabla\vec{u} + \nabla\frac{G}{1-2\nu}(\nabla \cdot \vec{u}) - \lambda\nabla \mathrm{N}(\bar{x},t) = 0 \quad (3).$$

N refers to the cell number, and $\vec{u}$ is a vector of displacements in the x and y directions. Equation (1) models the rate of tumor cell number change at a given spatiotemporal location as the sum of random cell diffusion and logistic growth. k is the tumor cell proliferation rate [6-8]. D is the cellular diffusion coefficient, which is coupled to tissue mechanics through Equation (2) [6-8]. In Equation (2), D_0 is the diffusion coefficient of tumor cells when there is no stress present, σ_{VM} is von Mises stress, and γ is an empirically derived coupling coefficient [6-8]. Equation (3) models the isotropic, linear elastic mechanical equilibrium which is undergoing an external expansive force [6-8]. This expansive force is the result of a coupling constant, λ, and changes in tumor cell number [6-8]. G represents shear modulus, and ν is the Poisson's ratio. Additional details are available in previous work [6-8].

The Galerkin Method of Weighted Residuals was used to spatially integrate the 2D domain of linear triangular elements [9]. Boundary conditions are enforced on the outermost mesh boundary, which is representative of the dura boundary with the skull. The boundary conditions are expressed in a normal/tangent-to-boundary coordinate reference allowing for conditions that restrict displacements in the normal direction but allow for slip tangentially.

This model is incorporated into the tumor parameter estimation framework as shown in Figure 1. T_1-weighted contrast enhanced images are selected based on lesion changes from the last two imaging time points. The images are rigidly registered using a normalized mutual information algorithm. The tumor cell number is estimated at both time points by manually segmenting the enhancing lesion and assuming a Gaussian distribution of tumor cell density. We then fit the model of tumor growth to the observed tumor cell number in the clinical scans using a Levenberg-Marquardt parameter optimization algorithm in MATLAB (MathWorks Inc., Natick, MA) to estimate D_0, the tumor cell diffusion coefficient, and k, the tumor cell proliferation rate. For the purposes of this study, both D_0, and k were considered as constant over the entire tumor domain.

This model-based framework treats all lesions as recurrent tumor with growth governed by Equations (1)-(3). We hypothesize that the differences in the biophysics of the lesions (recurrent tumor or radiation-induced necrosis) will lead to differences in the parameter estimates of the tumor growth model, D_0 and k.

3. RESULTS

The model was used to estimate tumor growth parameters for each patient, with known pathological confirmation of lesion etiology. For the patient with tumor recurrence, the model-estimated parameters were $D_0 = 1.93E-01\ mm^2/day$ and $k = 3.19E-02\ day^{-1}$. The model-estimated parameters for the patient with radiation-induced necrosis, were $D_0 = 5.15E-01\ mm^2/day$ and $k = -6.43E-02\ day^{-1}$. The results of the framework are visualized in Figures 2 and 3.

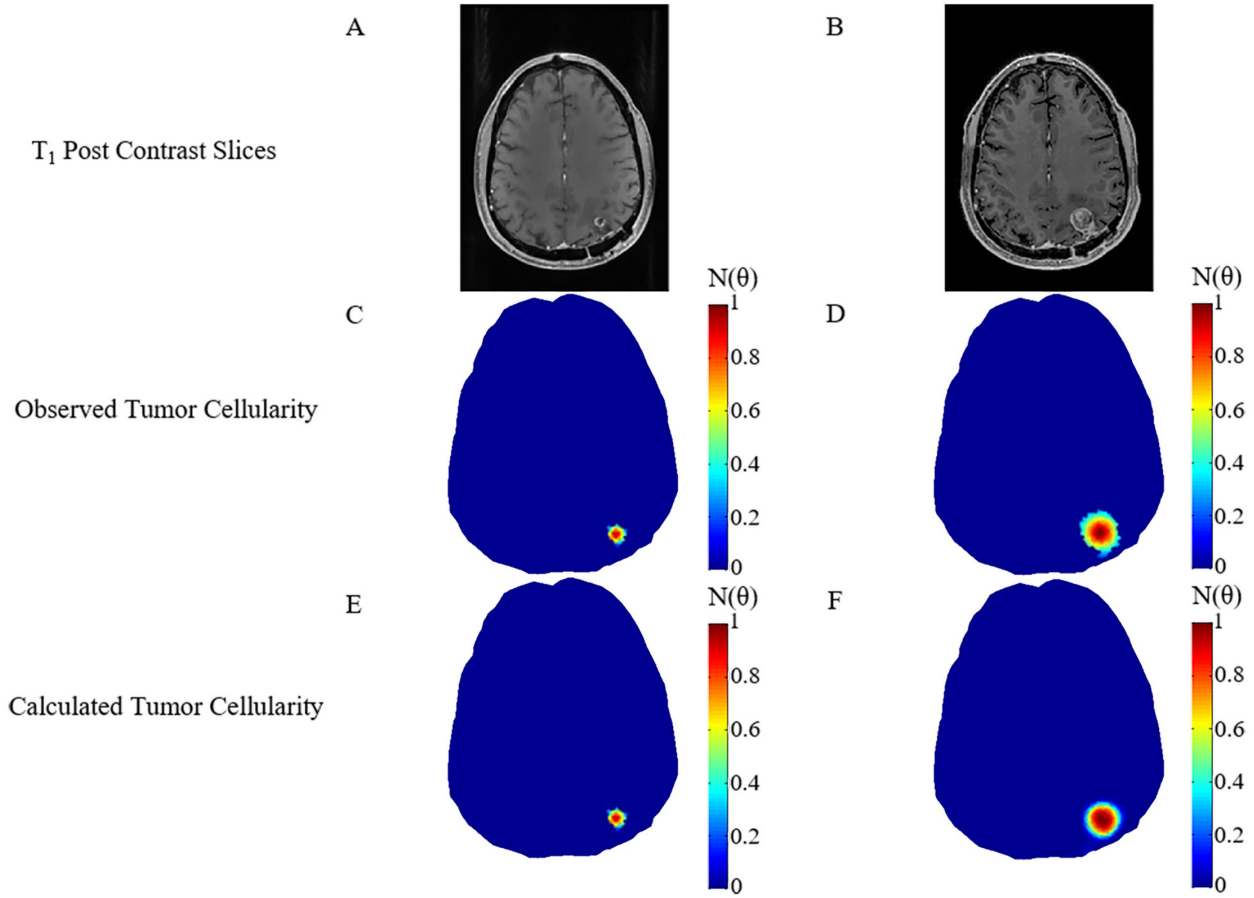

Figure 2. Post-contrast T_1-weighted MR imaging data (A,B), observational estimated tumor cellularity (C,D), and model-calculated tumor cellularity (E,F) for a patient with a lesion identified as tumor progression. Left column (A,C,E) represents the initial time point, and the right column (B,D,F) represents the final time point, prior to pathological confirmation of lesion etiology.

In both Figures 2 and 3, the images in the left and right columns represent the initial time point and the final time point respectively. Panels A and B are the axial slices of the T_1-weighted contrast enhanced scans. Panels C and D are images of the observed tumor cellularity determined by manual segmentation and the Gaussian tumor cell density assumption. Panels F are images of the model calculated tumor cellularity at the final time point, using the parameters calculated. Panel E is identical to Panel C, as the model is seeded with the initial observed tumor cell number.

Qualitatively, it is evident that changes in the enhancing lesion (Panels A and B), are very similar in imaging characteristics despite being different diagnoses. Comparing Panel D to Panel F, it is evident that in both etiologies, the model was able to fit reasonably to the patient-specific scans. This speaks to the mechanically-coupled reaction-diffusion model [6-8] as a reasonable approximation to these mass changes within the parenchyma.

4. CONCLUSIONS

The results of this preliminary investigation indicates promise that the framework outlined in this study may allow use of patient-specific clinical imaging data within a biophysical model of tumor growth to noninvasively differentiate between radiation-necrosis and tumor recurrence. The change in k from positive to negative, in the patient with recurrence and radiation-induced necrosis respectively potentially indicates the feasibility of differentiating the two conditions. The next step will be performing a retrospective study to determine the performance of the estimated tumor cell proliferation rate as a marker of lesion etiology in a large patient cohort. In this study, T_1-weighted contrast enhanced imaging was the only imaging data source analyzed. Often, patients with intracranial metastases receive serial imaging examinations with other imaging sequences. Understanding the use of other scan types as data sources to determine the existence of other comparators will be important. While the scope of the current study is limited, it demonstrates methodological proof-of-concept for the use of mechanically-coupled reaction-diffusion models initialized with clinical imaging data. This study also demonstrates the potential for biophysical model-based image analysis frameworks for use as a noninvasive diagnostic metric for patients who have previously undergone SRS and show lesions of unknown etiology on follow-up radiographic examinations.

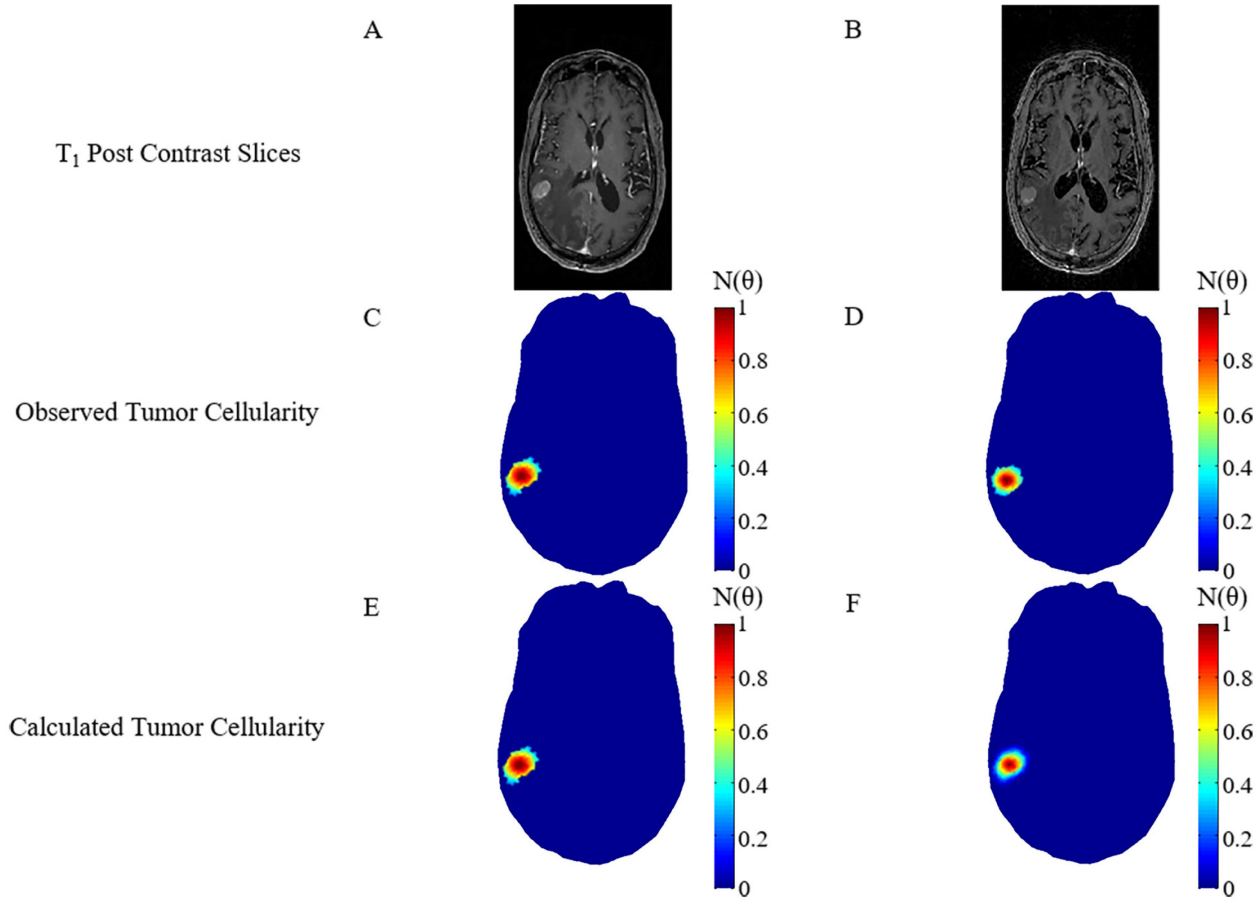

Figure 3. Post-contrast T_1-weighted MR imaging data (A,B), observational estimated tumor cellularity (C,D), and model-calculated tumor cellularity (E,F) for a patient with a lesion identified as radiation-induced necrosis. Left column (A,C,E) represents the initial time point, and the right column (B,D,F) represents the final time point, prior to pathological confirmation of lesion etiology.

5. ACKNOWLEDGEMENTS

This work is supported by the NIH-National Institute of Neurological Disorders and Stroke R01NS049251, NIH-National Cancer Institute K25CA204599, and the VISE Seed Grant program.

6. REFERENCES

[1] N. Verma, M.C. Cowperthwaite, M.G. Burnett, and M.K. Markey, "Differentiating tumor recurrence from treatment necrosis: a review of neuro-oncologic imaging strategies," *Neuro Oncol*, vol. 15, no. 5, pp. 515-34, May 2013.

[2] N.C. Atuegwu, L.R. Arlinghaus, X. Li, E.B. Welch, B.A. Chakravarthy, J.C. Gore, and T.E. Yankeelov, "Integration of diffusion-weighted MRI data and a simple mathematical model to predict breast tumor cellularity during neoadjuvant chemotherapy," *Magn Reson Med*, vol. 66, no. 6, pp. 1689-96, Dec. 2011.

[3] H.L. Harpold, E.C. Alvord, Jr., and K.R. Swanson, "The evolution of mathematical modeling of glioma proliferation and invasion," *J Neuropathol Exp Neurol*, vol. 66, no. 1, pp. 1-9, Jan. 2007.

[4] T.E. Yankeelov, N. Atuegwu, D. Hormuth, J.A. Weis, S.L. Barnes, M.I. Miga, E.C. Rericha, and V. Quaranta, "Clinically relevant modeling of tumor growth and treatment response," *Sci Transl Med*, vol. 5, no. 187, pp. 187ps9, May 2013.

[5] G. Helmlinger, P.A. Netti, H.C. Lichtenbeld, R.J. Melder, and R.K. Jain, "Solid stress inhibits the growth of multicellular tumor spheroids," *Nat Biotechnol*, vol. 15, no. 8, pp. 778-783, Aug. 1997.

[6] J.A. Weis, M.I. Miga, L.R. Arlinghaus, X. Li, A.B. Chakravarthy, V. Abramson, J. Farley, and T.E. Yankeelov, "A mechanically coupled reaction-diffusion model for predicting the response of breast tumors to neoadjuvant chemotherapy," *Phys Med Biol*, vol. 58, no. 17, pp. 5851-66, Sep. 2013.

[7] J.A. Weis, M.I. Miga, L.R. Arlinghaus, X. Li, V. Abramson, A.B. Chkravarthy, P. Pendyala, and T.E. Yankeelov, "Predicting the response of breast cancer to neoadjuvant therapy using a mechanically coupled reaction-diffusion model," *Cancer Res*, vol. 75, no. 22, pp. 4697-707, Nov. 2015.

[8] J.A. Weis, M.I. Miga, and T.E. Yankeelov, "Three-dimensional image-based mechanical modeling for predicting the response of breast cancer to neoadjuvant therapy," *Comput Methods Appl Mech Engrg*, vol. 314, pp. 494-512, Feb. 2017.

[9] Lynch, D.R., *Numerical Partial Differential Equations for Environmental Scientists and Engineers: A First Practical Course*, Springer Science & Business Media, New York, NY, 2005.